

### **REMARKS**

Applicant respectfully requests reconsideration of the claims in view of the following remarks. Claims 1 and 3-10 are pending. No amendments have been made to the claims in the present paper.

#### **Examiner Interview**

Applicant's representative Eric DeMaster (Regis. No. 55,107) contacted Examiner Yevegeny by telephone on November 13, 2009. Unexpected results regarding phototoxicity of vitamin K1 and the presently claimed oxide were discussed. Although no agreement was reached with respect to the allowability of the claims, the Examiner indicated the unexpected results regarding phototoxicity may be useful in overcoming the obviousness rejection. Applicant's undersigned representative thanks the Examiner for the courtesies extended during the telephonic interview. Unexpected results regarding phototoxicity are discussed below.

#### **Rejections under 35 U.S.C. § 103**

Claims 1 and 3-10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Elson (U.S. 5,510,391) in view of Dowd (*J. Am. Chem. Soc.*, 1991, 113:7734-7743) and further in view of Nagley (U.S. 5,981,601) and Larson (U.S. 6,180,136). Applicant respectfully traverses this rejection and submits that the combined prior art references do not disclose or suggest the presently claimed invention.

The Office Action alleges at page 4 that vitamin K1 oxide would be considered to be a species of the generic teaching of Elson. Applicant does not agree.

It is well established that "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984). The Elson reference discloses a method that can employ a vitamin K analog. This reference admits that the vitamin K analog is limited to "vitamins K-3, K-4, K-5, K-6, and K-7" (column 1, lines 37-39) and does not even mention oxides or epoxides. Moreover, each of the analogs disclosed in Elson has the common methylated naphthalene ring

which is aromatic and known to have some particular chemical behavior. In contrast, vitamin K1 oxide does not include this aromatic system, the presence of the epoxide breaks the aromatic. There is no teaching mentioned or suggested in Elson that would have led the person skilled in the art to break this aromatic ring which was known to have an importance for the properties of the vitamin K analogs discussed in Elson (vitamins K1, K2, K3, K4, K5, K6 and K7). Therefore, one of skill in the art would not have considered vitamin K oxide to be a vitamin K analog in view of the description of vitamin K analogs in the Elson reference.

The Office Action at page 5 alleges it would have been obvious to one of skill in the art to utilize vitamin K oxide instead of vitamin K for the treatment of dermatological lesions as an expectation of success is provided by Dowd, which allegedly discloses that vitamin k oxide is the active metabolite of vitamin K. Applicants do not agree.

All evidence bearing on the issue of obviousness must be considered and evaluated before the required legal conclusion is reached. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983). A prior art reference that teaches away from the claimed invention is a significant factor to be considered in determining obviousness. *In re Gurley*, 27 F.3d 551, 554 (Fed. Cir. 1994). Only after all evidence of nonobviousness has been considered can a conclusion on obviousness be reached. *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984).

As discussed in the declaration of Dr. Marchal filed herewith (hereinafter the Marchal Declaration), between 1964 and 1994 at least 52 patients with cutaneous adverse effects of vitamin K1 were described in the European and North American literature, with 94 cases in the Japanese literature. See the Marchal Declaration at paragraph 4. The cutaneous adverse reactions were found to split into two groups: reactions of eczema type and reactions of scleroderma type. See the Marchal Declaration at paragraph 4.

Between December 2003 and June 2004, five cutaneous adverse side effects of allergic nature resulting from the use of three cosmetic products containing vitamin K1 were reported to the French drug security administration Agence française de sécurité sanitaire des produits de santé (hereinafter "Afssaps"). In response, commercialization of these products was stopped by Afssaps and the manufacturing, commercialization, sale, and use of cosmetic products containing

vitamin K1 was prohibited in France. See the Marchal Declaration at paragraph 5. In response to the reports of cutaneous adverse effects of vitamin K1, the European Commission Scientific Committee on Consumer Products concluded that the use of vitamin K1 in cosmetic products is not safe. See the Marchal Declaration at paragraph 5.

The cutaneous adverse side effects were not limited to vitamin K1. Therapeutic application of the synthetic analogue vitamin K3 had previously been investigated and abandoned as application of vitamin K3 1% in an ointment base to the skin produced an irritant contact dermatitis. See the Marchal Declaration at paragraph 6.

In view of the knowledge within the field in at the time of filing of the PCT application (January 20, 2004) regarding cutaneous adverse side effects associated with the administration of vitamin K1 both topically and parenterally, one of skill in the art would not have considered vitamin K1 or a vitamin K1 analogue suitable for use in a composition, such as a crème, gel lotion, or liquid, for treating a dermatological lesion. See the Marchal Declaration at paragraph 7. Therefore, one of skill in the art would have considered Elson and Dowd in view of these teachings regarding adverse side effects and would not have combined Elson and Dowd as set forth in the Office Action as the known adverse side effects regarding cutaneous adverse side effects associated with the administration of vitamin K1 both topically and parenterally teaches away from the combination and away from using vitamin K1 or an analogue of vitamin K1 to treat dermatological lesions. The disclosures of the Nagley and Larson references do not cure the deficiencies of Elson and Dowd for the same reasons.

The Office Action at pages 5 and 6 alleges that Applicant has conceded that the prior art recognized that vitamin K oxide creams are more topically active than vitamin K creams. Applicants do not agree.

As discussed in the declaration of Dr. Karavani filed herewith (hereinafter the Karavani Declaration), the statements in the Office Action regarding what was recognized in the prior art is not correct as neither the study of Exhibit A nor the studies referred to by Dr. Karavani at lines 7-8 of the Pharmacological aspects section of Exhibit A were publicly available prior to the filing date (January 20, 2004) of international application no. PCT/BE/04/0011, from which the present application claims priority. Absent Applicant's disclosure, the Office Action has not

provided any evidence that vitamin K oxide creams were known to be more topically active than vitamin K creams

Dr. Karavani was retained by the inventor, Dr. Alfred Marchal, as an expert to perform experimental studies for the assignee Auriga International. One of the studies Dr. Karavani performed for the assignee was the study of Exhibit A entitled "Topical use of vitamin K oxide: A clinical evaluation of postoperative bruising and edema." This study was transmitted to the assignee by Dr. Karavani and was not publicly disclosed prior to the filing date of the PCT application. See the Karavani declaration at paragraph 4.

As an expert for the assignee, other experimental studies performed for the assignee were made available to Dr. Karavani. See the Karavani declaration at paragraph 5. The studies that Dr. Karavani was referring to at lines 7-8 of the Pharmacological aspects section of Exhibit A were experimental studies performed for the assignee which evaluated vitamin K1 oxide compared to vitamin K1 for treating bruising (ecchymosis). See the Karavani declaration at paragraph 5. In these studies, cosmetic creams containing vitamin K oxide were found to be more topically active than cosmetic creams containing vitamin K. These studies were provided by the assignee to Dr. Karavani in his capacity as an expert for the assignee and were not publicly disclosed prior to the filing date of the PCT application. See the Karavani declaration at paragraph 5.

Applicant therefore submits the studies referenced at lines 7-8 of the Pharmacological aspects section of Exhibit A are not prior art. Applicant has not otherwise conceded or admitted that vitamin K oxide creams were known to be more topically active than vitamin K creams.

### **Unexpected Results**

The Office Action suggests that unexpected results for the claimed compound compared to the prior art can overcome the obviousness rejection.

At the time of filing of the PCT application (January 20, 2004), vitamin K1 was known to be unstable in a cosmetic product when exposed to UV light and unsafe in a cosmetic product as it may cause cutaneous allergy. In view of the known photoinstability and toxicity of vitamin K1

in cosmetic products, Dr. Marchal conducted a study in 2003 to determine if vitamin K1 and vitamin K1 oxide were phototoxic to epidermis. See the Marchal Declaration at paragraph 8.

A phototoxicity assay was carried out using SKINETHIC™ human reconstituted epidermis (REps). A fully differentiated epithelium having the features of human epidermis was obtained by culturing human keratinocytes in a chemically-defined medium on inert microporous polycarbonate filters at the air-liquid interface. See the Marchal Declaration at paragraph 9. Vitamin K1 and vitamin K1 oxide were tested undiluted (i.e. 100%) and diluted to 10% and 1% (v/v) in paraffin oil. The vitamin K1 or vitamin K1 oxide was directly applied to the culture surface on the dry stratum corneum of epidermis and the toxic effect of vitamin K and vitamin K1 oxide was assessed using the MTT assay. See the Marchal Declaration at paragraph 9. Results under non-UV conditions are shown in Table 1.

Table 1

<b>Vitamin K1</b>	
Concentration [% (v/v)]	Viability (%)
0	100
1	96
10	93
100	93
<b>Vitamin K1 oxide</b>	
Concentration [% (v/v)]	Viability (%)
0	100
1	90
10	91
100	100

As shown in Table 1, no significant cytotoxicity was observed in REps exposed to vitamin K1 or vitamin K1 oxide at the tested concentrations.

Undiluted (100% v/v) vitamin K1 or vitamin K1 oxide was applied to REps and incubated 24 hours prior to UV<sub>A</sub> irradiation. See the Marchal Declaration at paragraph 10. The results under UV and non-UV conditions are shown in Table 2.

Table2

Vitamin K1			
Viability (%)	Cytotoxicity (%)	Concentration [% (v/v)]	UV <sub>A</sub> irradiation
100	0	0	
97	3	0	6 J/cm <sup>2</sup>
100	0	100	
38	62	100	6 J/cm <sup>2</sup>
Vitamin K1 oxide			
Viability (%)	Cytotoxicity (%)	Concentration [% (v/v)]	UV <sub>A</sub> irradiation
100	0	0	
97	3	0	6 J/cm <sup>2</sup>
100	0	100	
99	1	100	6 J/cm <sup>2</sup>

As shown in Table 2, the viability of REps treated with vitamin K1 in UV<sub>A</sub> irradiation conditions as compared to non-UV conditions was markedly decreased. These results indicated that vitamin K1 is phototoxic. See the Marchal Declaration at paragraph 11. In contrast, the viability of REps treated with vitamin K1 oxide in UV<sub>A</sub> irradiation conditions was comparable to that in non-UV conditions.

If vitamin K1 oxide were an analogue of vitamin K, it would be expected that vitamin K1 oxide would have activity in the phototoxicity assay similar to vitamin K1. See the Marchal Declaration at paragraph 12. The results in Table 2 show that vitamin K1 oxide is not phototoxic. These results were unexpected in view of the vitamin K1 results, which show that vitamin K1 is phototoxic. See the Marchal Declaration at paragraph 12. Accordingly, the presently claimed vitamin K oxide exhibits an unexpected result compared to the prior art vitamin K1. Thus, this rejection should be withdrawn.

## Conclusion

Accordingly, based on the foregoing differences, Applicant respectfully submits that the presently claimed methods are neither taught nor suggested by the references cited in this rejection, and withdrawal of this rejection is earnestly solicited.

## Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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